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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
FEB 81 M J TOPPER, M H WEEKS
USAEHA-75-51-0144-81

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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT

AI3-37443a

US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL

STUDY NO. 75-51-0144-81

SEPTEMBER 1978 - NOVEMBER 1980

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluation of AI3-37443a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical did not cause skin, eye, or photo irritation. It did not prove to be a skin sensitizer or to be acutely toxic by ingestion. It was recommended that the chemical be approved for further testing as a candidate insect repellent.			

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U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Topper/ldr/AUTOVON
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HSE-LT-T/WP

5 FEB 1981

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
AI3-37443a, US Department of Agriculture Proprietary Chemical,
Study No. 75-51-0144-81, September 1978 - November 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluation of AI3-37443a was performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. The technical grade chemical did not cause skin, eye, or photo irritation. It did not prove to be a skin sensitizer or to be acutely toxic by ingestion. It was recommended that the chemical be approved for further testing as a candidate insect repellent.

FOR THE COMMANDER:

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as (5 cy)

John F. Mazur
JOHN F. MAZUR
MAJ, MSC
Director, Laboratory Services

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Cen on Tox, NRC
Comdt, AHS (HSA-IPM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region

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4. Not Applicable	
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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT
AI3-37443a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICAL
STUDY NO. 75-51-0144-81
SEPTEMBER 1978 - NOVEMBER 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 13 September 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of candidate insect repellent AI3-37443a.

4. SUMMARY OF FINDINGS. Hazard evaluation of the candidate repellent AI3-37443a, US Department of Agriculture (USDA) Proprietary Chemical, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study No. 75-51-0144-81, Sep 78 - Nov 80

TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Chemical A13-37443a did not cause any irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A).
0.5 mL technical grade chemical applied to each of six rabbits.	Details are shown in Appendix B.	
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of six New Zealand White rabbits.	Chemical A13-37443a did not cause any irritation to the eyes of rabbits. Details are shown in Appendix C.	USAEHA Category A (ref Appendix A).
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD = 2900 mg/Kg	Presents little lethal hazard from accidental ingestion.

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Test	Results	Interpretation
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PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25 percent (w/v) solution of each chemical and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	A 25 percent solution of AI3-3743a in ethanol did not cause a photochemical irritation reaction under test conditions. Ethanol solution of AI3-37443a caused moderate erythematous and edematous reactions on both non-UV and UV skin sites.	Chemical AI3-37443a did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation in humans.
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Control

Following UV exposures of the rabbits, 0.05 mL of test chemical, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48, and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas. Details are shown in Appendix D.	Ethanol solutions of this chemical may cause moderate skin irritation in sensitive individuals. Persons experiencing this reaction should wash off the solution as soon as possible.
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Test	Results	Interpretation
<u>SENSITIZATION STUDIES</u>		
<u>Guinea Pigs (Male)</u>		
Intradermal injection of 0.1 mL of a 0.1 percent solution (w/v) of AI3-37443a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of each test chemical.	Challenge doses of AI3-37443a did not produce a sensitization reaction.	Chemicals AI3-37443a did not produce sensitization reactions under test conditions and is not expected to produce sensitization reactions in man.
Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB produced a marked sensitization reaction in 10 out of 10 guinea pigs. Details are shown in Appendix E.	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer.

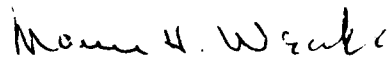
Study No. 75-51-0144-81, Sep 78 - Nov 80

5. CONCLUSION. Technical grade chemical AI3-37443a did not cause any skin, eye, or photo irritation, no sensitization reaction, and did not prove to be an acute ingestion hazard.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-37443a be approved for further testing as a candidate insect repellent. Persons experiencing irritation when working with ethanol solutions of AI3-37443a should wash the site with copious amounts of water.



MICHAEL J. TOPPER, DVM
CPT, VC
General Veterinary Officer
Toxicology Division



MAURICE H. WEEKS
Chief, Toxicity Evaluation Branch
Toxicology Division

APPROVED:



ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

APPENDIX B

COMPOUND: AI3-37443a - USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0144-81			
PRIMARY SKIN EFFECTS NEW ZEALAND WHITE RABBITS		TOXICITY CATEGORY AEHA I		CONDITIONS - 0.5 mL of technical grade chemical applied under 2" by 2" gauze patch for 24 hours.			
Time of Observation (Hours)	Response				Total Score	Comments	
	477	478	479	480 481 482			
<u>Erythema & Eschar</u>							
Intact Skin				2	0	3	
Intact Skin				0	0	0	
Abraded Skin	1		2	1		5	
Abraded Skin	0		1	0		1	
						<u>9</u>	
						Subtotal	
<u>Edema Formulation</u>							
Intact Skin		0		0	0	0	
Intact Skin		0		0	0	0	
Abraded Skin	1		0		0	1	
Abraded Skin	0		0		0	0	
						<u>1</u>	
						Subtotal	
						<u>10</u>	
						Total	

APPENDIX C

COMPOUND: AI3-37443a - USDA Proprietary Chemical										USAEHA STUDY No. 75-51-0144-81									
ACUTE EYE EFFECTS NEW ZEALAND WHITE RABBITS					TOXICITY CATEGORY AEHA A					CONDITIONS - 0.1 mL of chemical instilled in conjunctival sac of left eye of each rabbit. No rinse.									
Time of Reading Hrs-Days	Structure	Scores Rabbit No.								Mean Score	Comments								
		324	325	326	327	328	329												
24	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 1	0 0 0		0 0 0.2										
48	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0		0 0 0										
72	cornea iris conjunctivae	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0		0 0 0										
7-days	cornea iris conjunctivae																		

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APPENDIX D

COMPOUND: AI3-37443a - USDA Proprietary Chemical USAEHA Study No. 75-51-0144-81

PHOTO CHEMICAL
IRRITATIONComments: Moderately irritating in 95% ethyl alcohol
with or without UV exposure.NEW ZEALAND WHITE
RABBITSProcedure: 0.05 mL of a 25% solution of compound in 95% ethanol are applied to
two sites on back of rabbit. One compound is exposed to UV light for
30 minutes. 0.05 mL of a 10% solution of bergamot oil is a positive
control.

Mean Skin Irritation Score

Observation Time	Test Compound		Positive Control		Positive Control	
	Erythema	Edema	No UV Exposure	UV Exposure	No UV exposure	UV exposure
24 Hours	2.0	2.5	2.0	1.8	1.0	0.3
48 Hours	2.0	1.7	1.8	1.7	0.2	0.0
72 Hours	2.0	1.3	2.0	1.8	0.2	0.0
Total Mean Irritant Responses	2.0	1.8	1.9	1.7	0.8	0.1

APPENDIX E

COMPOUND: AI3-37443a, USDA Proprietary Chemical				USAEHA STUDY NO. 75-51-0144-81			
GUINEA PIG SENSITIZATION MALE HARTLEY STRAIN				Substance: Injected 0.1 mL intradermally of a 3% suspension of AI3-37443a Identify: AI3-37443a Positive Control: Dinitrochlorobenzene			
Scoring Time 24 hours	Mean Body Wt (G)		Mean Irritation Scores				Comments
	Initial	Final	Diluent		Test Compound		
Test Compound	487 + 48	713 + 72	0.0	0.0	1.8	1.8	
Positive Control	491 + 29	736 + 56	0.0	0.0	1.8	356	
Test Compd 48 hours	Mean Body Wt (G)		Mean Irritation Scores				Final Scores >100 - Strong Sensitizing 25-100 - Mild Sensitizing <25 - No Sensitizing
	Initial	Final	Diluent		Test Compound		
Test Compound	---	---	0	0	0.4	0.6	
Positive Control	---	---	0	0	5	272	

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